Access to high rotational barrier atropisomers

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Abstract

The today's drug discovery is profoundly affected by chirality; enantiomers may differ significantly in biological activity with tremendous impact. Atropisomerism is a type of axial chirality resulting from hindered rotation of a σ bond that yields non superimposable stereoisomers (coined as "atropisomers"). The phenonemenon has been widely applied in materials, asymmetric organic synthesis and of course pharmaceuticals. Most of the atropisomers have low energy barriers (*class 1, ΔE_{rot} < 20 kcal/mol*), thus rapidly equilibrating. Nowadays, in drug discovery, it is almost prohibited to synthesize class 2 atropisomers (ΔE_{rot} ≈ *20-30 kcal/mol*), whereas it is highly recommended that molecules with one or more atropisomeric axes has to be developed as class 3 *(>30 kcal/mol*). However, the synthetic access to such molecules might be extremely challenging [1,2].

Herein, we would like to report for the first time, a synthetic access to high rotational barrier atropisomers via multicomponent reaction chemistry (MCRs). A novel class of atropisomers is reported through a Ugi-tetrazole multicomponent reaction (UT-4CR) using various aromatic and polyaromatic aldehydes, benzylamine, ortho-substituted phenyl isocyanides and trimethyl silyl azide to afford the corresponding products in high yields (Scheme 1). Several single crystal structures have been obtained demonstrating the effect, combined with DFT calculations and NMR studies.

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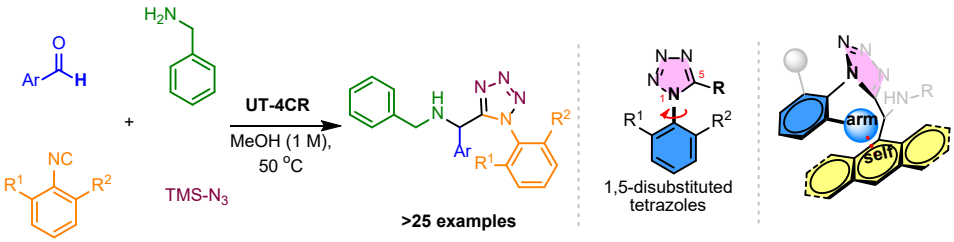

Scheme 1. Access to atropisomers via MCRs; the development of hetero biaryl atropisomers based on the UT-4CR

References

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